Remarks

Upon entry of this amendment, claims 21-25, 28-44, 47-51, 54-78, 80-84, 87-103, 106-110, 113-119, 122-137, and 139-198 will be pending in the above-captioned application.

Claims 33, 67, 92, 126, 161, and 177 have been amended to recite the antibody or fragment thereof "further comprising a label." Support for this amendment can be found in the specification as filed, *e.g.*, at page 97, paragraphs 244-246.

Claims 41, 75, 100, and 134 have been amended to recite a fused antibody or fragment thereof wherein the antibody or fragment thereof of the invention is fused to heterologous polypeptide. Support for this amendment can be found in the specification as filed, *e.g.*, at page 90, paragraph 222 to page 91, paragraph 223.

Accordingly, no new matter has been introduced and entry of this amendment is respectfully solicited.

I. Allowable Claims

Applicants thank the Examiner for indicating that claims 21-25, 28-29, 32, 38-40, 42-43, 56-60, 63-64, 66, 72-74, 76-77, 80-84, 87-88, 91, 97-99, 101-102, 115-119, 122-123, 125, 131-133, 135-136, 139, 142-157, 160, 166-173, 176, 182-188, and 194-198 are allowable. *See*, Paper No. 20031026, page 3, paragraph 7.

II. Indefiniteness Rejections Under 35 U.S.C. § 112, Second Paragraph

A. Claims 30, 65, 89, 124, 141, and 158

The Examiner has rejected claims 30, 65, 89, 124, 141, and 158 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the term "fragment thereof" is ambiguous because "only intact antibody can be a human antibody and not an antibody fragment." *See*, Paper No. 20031026, page 2, paragraph 6A.

Applicants respectfully disagree and traverse.

Applicants assert that it was well recognized in the field of immunology that the term "human" depends on whether the sequence is derived from a human and not on its length. Thus, if the antibody or fragment thereof is completely derived from a human sequence, the skilled artisan would call that antibody or fragment thereof "human". Moreover, Applicants contend that human antibody fragments were well-known in the art

as of the earliest filing date of the present application. For example, it was well-known that a skilled artisan could use a protease, such as papain, with limited digestion to cleave an antibody into three fragments. (*See*, Janeway, C. & P. Travers. (1994) *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London), pg. 3:5, attached hereto as Exhibit A).

In addition, these fragments, such as Fab fragments, were commonly produced and used in the art at the time of the earliest filing of the instant application. (*See*, Kang, A.S. *et al.*, "Linkage of recognition and replication functions by assembling combinatorial antibody Fab libraries along phage surfaces," *P.N.A.S.* 88:4363-4366 (1991); and Persson, M.A.A. *et al.*, "Generation of diverse high-affinity human monoclonal antibodies by repertoire cloning," *P.N.A.S.* 88:2432-2436 (1991), attached hereto as Exhibits B and C, respectively). These publications show two different approaches, phage library screening and repertoire cloning, to generate functional human antibody fragments. Thus, Applicants assert that the term "fragment thereof" in combination with "human" was well understood in the art at the time of the earliest filing of the instant application. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 30, 65, 89, 124, 141, and 158 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness.

B. Claims 31, 90, 159, and 174

The Examiner has also rejected claims 31, 90, 159, and 174 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the term "fragment thereof" is ambiguous because "only intact antibody can be a polyclonal antibody and not an antibody fragment." *See*, Paper No. 20031026, page 2, paragraph 6B.

Applicants respectfully disagree and traverse.

Applicants assert that the term "polyclonal" is a well-known term in the art that refers to an antibody's binding sites and specificity, not to its size. For example, a common definition of polyclonal is in association with activation by an antigen. As defined in a well-known Immunology textbook by Janeway and Travers, polyclonal activation involves "multiple clones of diverse specificity." (*See*, Janeway, C. & P. Travers. (1994) *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London), Glossary, pg. G:15, attached hereto as Exhibit D). Thus, the skilled artisan recognizes that any antibody, regardless of whether it is an

intact antibody or a fragment, may be "polyclonal" if it contains multiple antigen binding sites.

Accordingly, Applicants contend that a skilled artisan would clearly recognize that a polyclonal antibody is not limited to the intact antibody, but can also encompass a fragment thereof. Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 31, 90, 159, and 174 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness.

C. Claims 54, 113, 140, and 175

The Examiner has further rejected claims 54, 113, 140, and 175 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the term "fragment thereof" is ambiguous because "only intact antibody can be a monoclonal antibody and not an antibody fragment." *See*, Paper No. 20031026, page 2, paragraph 6C.

Applicants respectfully disagree and traverse.

Similar to the argument set forth in Section II(B), Applicants contend that the term "monoclonal" is also a well-known term in the art that refers to an antibody's binding sites and specificity, not to its size. For example, monoclonal antibodies are defined as "homogenous antibodies derived from a single-antibody producing cell," (*See*, Janeway, C. & P. Travers. (1994) *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London), pg. 2:5, attached hereto as Exhibit E). Once again, Applicants assert that there is no indication in the art that a fragment of an antibody can not be monoclonal. Rather, as discussed in Persson *et al.* (attached hereto as Exhibit B), monoclonal Fab fragments were well-known and understood in the art a the time of the earliest filing of the instant application. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 54, 113, 140, and 175 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness.

D. Claims 44, 78, 103, and 137

The Examiner has further rejected claims 44, 78, 103, and 137 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the term "fragment thereof" is ambiguous because "hybridoma does not produce antibody

fragment, hybridoma produce only a whole intact antibody." *See*, Paper No. 20031026, page 3, paragraph 6D.

Applicants respectfully disagree and traverse.

Preliminarily, it is well-known in the art that antibodies consist of heavy and light chains further composed of variable and constant regions. (*See, e.g.*, Janeway, C. & P. Travers. (1994) *Immunobiology: The Immune System in Health and Disease*, (Current Biology Ltd./Garland Publishing, London), pp. 3:2-3:3, attached hereto as Exhibit F). Thus, an isolated, or "free" light chain is a fragment of the intact antibody.

Applicants assert that it was well-known in the art prior to the date of the earliest filing of the instant application that hybridoma can antibody fragments. For example, Ochi *et al.*, has shown that specific heavy and light chains can be produced from a hybridoma cell line. (See, Ochi *et al.*, "Functional immunoglobulin production after transfection of cloned immunoglobulin heavy and light chain genes into lymphoid cells," *P.N.A.S.*, 80:6351-6355 (1983), attached hereto as Exhibit G). Thus, the skilled artisan would have clearly understood that a hybridoma can produce not only intact antibodies, but also antibody fragments. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 44, 78, 103, and 137 for alleged lack of indefiniteness.

E. Claims 47, 106, and 189-193

The Examiner has further rejected claims 47, 106, and 189-193 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the term "fragment thereof" is ambiguous because "only antibody, not antibody fragment, can be obtained from animal that has been immunized with a protein." *See*, Paper No. 20031026, page 3, paragraph 6E.

Applicants respectfully disagree and traverse.

Applicants assert that the concept of an antibody fragment being secreted from an animal was well-known in the art at the time of the earliest filing of the instant application. For example, Applicants note that Urine Bence Jones proteins were well-known in the art prior to 1997. Bence Jones proteins are monoclonal antibody light chains that have been found in the urine of approximately 60% of human multiple myeloma patients. (*See*, Paul, S. *et al.*, "Natural catalytic antibodies: peptide-hydrolyzing activities of Bence Jones proteins and VL fragments," *J. Biol. Chem.*, 27(25):15257-15261 (1995), attached hereto

as Exhibit H). In addition, it was also known that transgenic animals can be engineered to express various human antibody fragments. (*See*, Choi *et al.*, "Transgenic mice containing a human heavy chain immunoglobulin gene fragment cloned in a yeast artificial chromosome," *Nature Genetics*, 4:117-122 (1993), attached hereto as Exhibit I). It was further known that immunization of such animals with an antigen can result in the production of such antibody fragments. Thus, it is well-documented in the art that, contrary to the Examiner's arguments, antibody fragments, in addition to intact antibodies, can be secreted from and obtained from an animal, including a human. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 47, 106, and 189-193 for alleged lack of definiteness.

F. Claims 33-37, 67-71, 92-96, 126-130, 161-165, and 177-181

The Examiner has also rejected claims 33-37, 67-71, 92-96, 126-130, 161-165, and 177-181 under 35 U.S.C. § 112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the claims at issue lack antecedent basis for a label. *See*, Paper No. 20031026, page 3, paragraph 6F.

Applicants respectfully disagree. However, Applicants have amended claims 33-37, 67-71, 92-96, 126-130, 161-165, and 177-181 to recite that the antibody or fragment thereof further comprises a label, thereby obviating the Examiner's rejection. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 33-37, 67-71, 92-96, 126-130, 161-165, and 177-181 under 35 U.S.C. § 112, second paragraph for an alleged lack of definiteness.

G. Claims 41, 75, 100, and 134

The Examiner has also rejected claims 41, 75, 100, and 134 under 35 U.S.C. §112, second paragraph for alleged indefiniteness. In particular, the Examiner alleges that the claims at issue have no antecedent basis for a fusion antibody. *See*, Paper No. 20031026, page 3, paragraph 6G.

Applicants respectfully disagree. However, as suggested by the Examiner, Applicants have amended claims 41, 75, 100, and 134 to recite "a fused antibody or fragment thereof" where the antibody or fragment of the invention is "fused to a heterologous polypeptide", thereby obviating the Examiner's rejection. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of

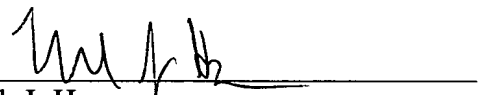
claims 41, 75, 100, and 134 under 35 U.S.C. § 112, second paragraph for an alleged lack of definiteness.

Conclusion

Applicants respectfully request that the above-made remarks and amendments be entered and made of record in the file history of the instant application. In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicants would expedite the allowance of this application. If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: March 1, 2004

Respectfully submitted,

By 

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